Pentannulation Reaction by Tandem Gold(I)-Catalyzed Propargyl Claisen Rearrangement/Nazarov Cyclization of Enynyl Vinyl Ethers.

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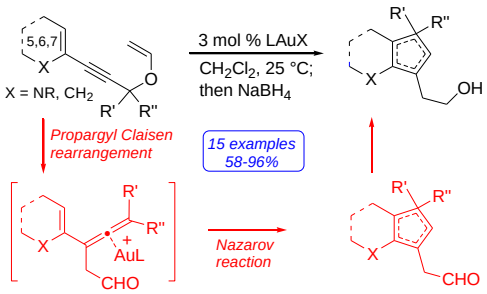
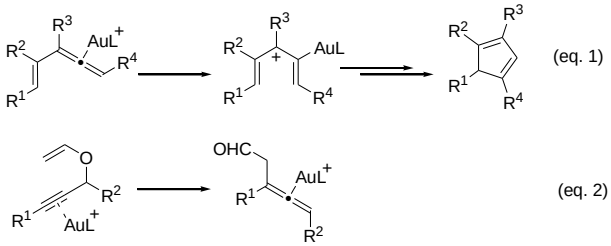
Supporting Information Placeholder



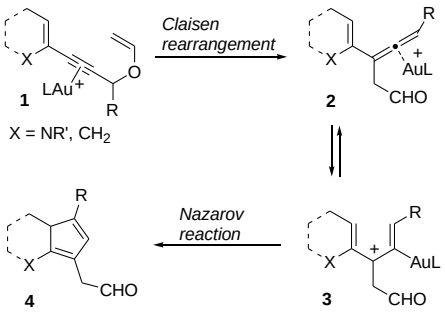
ABSTRACT: The tandem gold(I)-catalyzed propargyl Claisen rearrangement/Nazarov cyclization of propargyl vinyl ether derivatives, followed by in situ reduction of the resulting carbonyl group, provides functionalized cyclopentadienes fused with various N-hetero- and carbacycles, including indoles, in good to excellent yields. The reaction occurs with high regioselectivity, with the position of the double bonds in the five-membered ring which depends on the type of (hetero)cycle bearing the propargylic moiety and the side chain on the latter.

The Nazarov reaction, in its classical version, is the Lewis- or Brønsted acid-catalyzed 4π-electrocyclization of 1,4-dien-3-ones to form cyclopentenones.[1,2] The Nazarov reaction has now become one of the most important and versatile tool for the construction of 5-membered rings,[3] as in the last two decades a number of innovative approaches have been developed for the generation of the requisite pentadienyl cation undergoing the cyclization process.[4] Suitably functionalized allenes in particular have proved very useful as substrates for the Nazarov reaction under a variety of conditions, including treatment with oxidants, Brønsted acids, and transition-metal complexes.[4a,5]



Gold-catalyzed cycloisomerization of aryl allenes[6] and vinyl allenes (eq 1)[7,8] were first reported in 2006 and 2007, respectively, and were later exploited for the synthesis of pentannulated carba- and heterocycles.[9] Gold(I)-catalyzed cascade processes in which allene intermediates are generated by formal [3,3]-rearrangement of 5-acyloxy-1,3-enynes[10] have also been reported to efficiently provide 5-membered rings through a final Nazarov cyclization step.[9a-b,11,12]

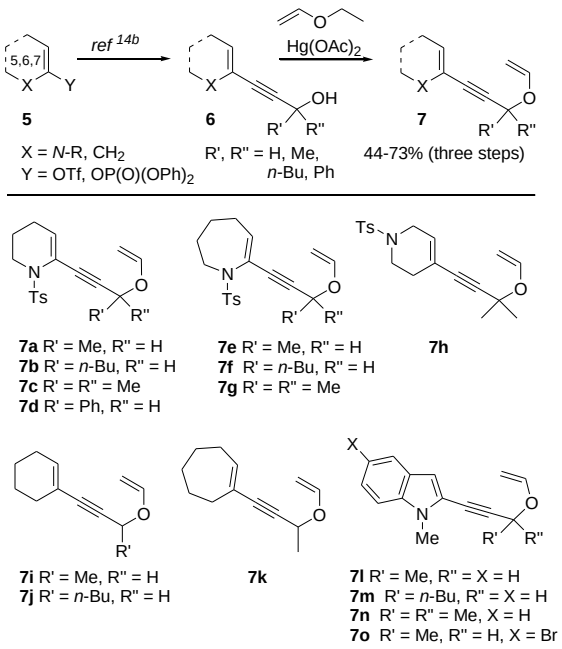
Scheme 1. Proposed tandem process



Due to our interest in the synthesis of cyclopenta-fused heterocycles by the Nazarov reaction[13], we recently extended the latter approach to the pentannulation of N-heterocycles[14] and the synthesis of natural compounds.[14a, 15]

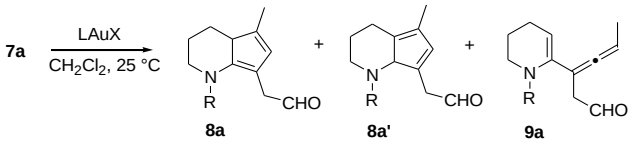
However, allenes can be prepared not only from propargylic acetates but also by the gold-catalyzed [3,3]-rearrangement of propargyl vinyl ethers (propargyl Claisen rearrangement, eq 2).[16] We envisaged that this reaction could be included in an unprecedented tandem process entailing a final Nazarov cyclization for the generation of cyclopentadienes (Scheme 1).[17] Thus, a suitably built enynyl vinyl ether (**1**), upon treatment with a gold catalyst, rearranges to give the corresponding allene-gold(I) complex (**2**). This, in turn, should generate the requisite pentadienyl cation intermediate (**3**) which cyclizes to ultimately form the target pentannulated compound (**4**). While with the rearrangement of enynyl acetates the final products are cyclopentenones, this process provides cyclopentadienes bearing, on the side chain, an aldehyde group which could be subjected to further elaboration, even in situ, for chain elongations or other transformations. For this study we decided to use substrates embodying the enynyl double bond in various *N*-heterocycles, including indoles, and carbacycles (compounds **7**, Scheme 2), so that the corresponding pentannulated products could eventually be obtained.

Scheme 2. Preparation of the substrates



The required enynyl vinyl ethers **7** were prepared by the Sonogashira reaction of either vinyl triflates or phosphates **5**, obtained from the corresponding lactams and cycloalkanones, with differently substituted propargyl alcohols, followed by *O*-vinylation[18] of the coupling products **6** (Scheme 2).[19] In order to find the optimal reaction conditions for the Au(I)-catalyzed tandem process, we subjected *N*-Ts-protected compound **7a** to a variety of conditions (Table 1), starting with those reported for the cycloisomerization of vinyl allenes[7] and the propargyl Claisen rearrangement.[16] Using 3 mol % $Ph_3PAuSbF_6$ in CH_2Cl_2 (Table 1, entry 1) the reaction was complete in 1 h and provided target compound **8a** (and its minor isomer **8a'**, formed during the aqueous work-up) as the major product (74%), but in mixture with allene **9a** (17%).[20] With BF_4^- as the counterion,[16] the reaction was similarly sluggish, being still incomplete after 5 h and providing a mixture of starting material, product **8**, and allene **9a**[21] (entry 2). Using TfO^- as the anion (entry 3), the reaction was instead much faster (0.5 h) and yielded **8** only. With an electron-poor ligand such as the phosphite $[(2,4\text{-di-}t\text{-}BuC_6H_3)O]_3P$ (entry 4) the reaction was much slower, conversion of **7a** into products (mainly allene **9a**) being 16% only. With $t\text{-}Bu_3PAuNTf_2$ as the catalyst (entry 5) the reaction was complete in 1.5 h, providing aldehyde **8** only. We carried out also a series of experiments with the NHC ligand IPr (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) and various anions and in all cases the reaction provided the **8a**/**8a'** mixture only (entries 6-10). Again, the reaction was faster with TfO^- as the non-coordinating anion (entry 8), being complete in 15 min. With this NHC ligand, we never observed allene **9a** when monitoring the reactions by ^1H NMR, even when carrying out the reaction at 0 °C (for example, only the signals of the starting material and the Nazarov product were present in the ^1H NMR spectrum at a 54% conversion, entry 6), or when the reaction was slow because of the anion used (entry 10),[23] which suggests a very fast cyclization of the gold-allene complex once formed under these conditions. The use of $AgSbF_6$ alone caused mainly devinylation of the starting material (entry 11).

Table 1. Optimization of the reaction conditions[a]



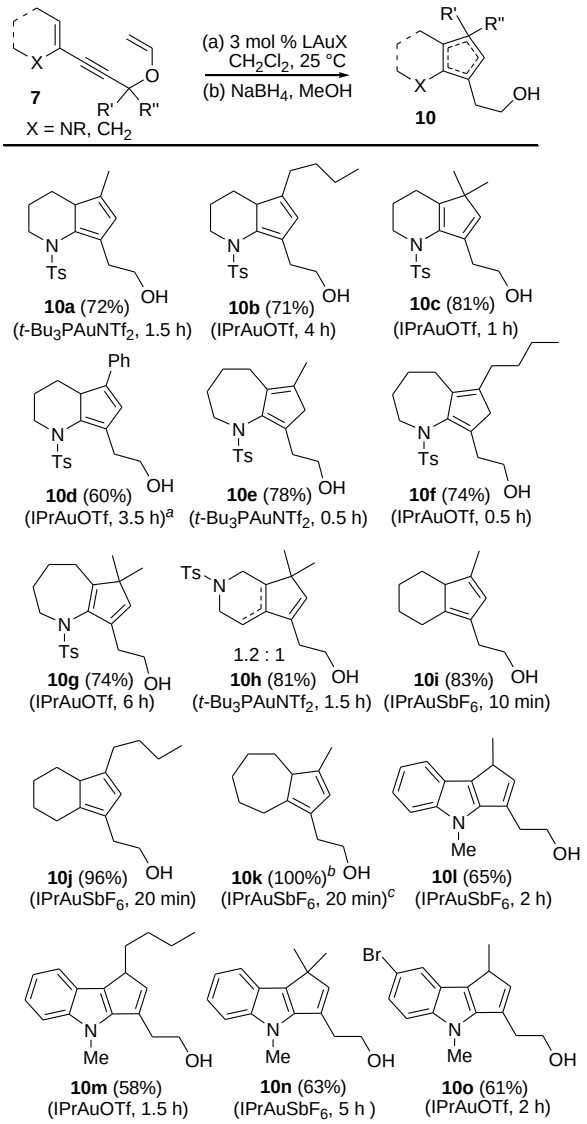
entry	catalyst[b]	time (h)	**7a**[c] (%)	**8a**[c] (%)	**8a'** (%)[c,d]	**9a**[c] (%)
1	$Ph_3PAuSbF_6$	1	-	74	9	17
2	Ph_3PAuBF_4	5	37	29	5	29
3	$Ph_3PAuOTf$	0.5	-	96	4	-
4	$[(2,4\text{-di-}{}^t\text{BuC}_6\text{H}_3)\text{O}]_3\text{P AuSbF}_6$	4	84	1	3	12
5	$t\text{-}Bu_3PAuNTf_2$[e]	1.5	-	95	5	-
6[f]	$IPrAuSbF_6$	3.5	46	49	5	-
7	$IPrAuSbF_6$	2.5	-	92	8	-
8	IPrAuOTf	0.25	-	94	6	-
9	$IPrAuNTf_2$[e]	1.5	-	78	22	-
10	$IPrAuBF_4$	3.5	31	54	15	-
11	$AgSbF_6$	1	-[g]	-	-	21

[a]*Conditions*: Reactions carried out on 0.2-0.3 mmol of **7a** in CH_2Cl_2 (0.05 M) at 25 °C under N_2 atmosphere. [b]Prepared by mixing the silver salt (AgX) and the gold chloride (LAuCl) in CH_2Cl_2 before addition of the substrate. [c]Relative amount determined by ^1H NMR of the crude reaction mixture. [d]Formed during the work-up. [e]Commercially available. [f]Carried out a 0°C. [g] Devinylation to form alcohol **6a** (79%) occurred to a great extent.

In assessing the scope of the reaction, because of the instability of the aldehydes during the chromatographic purification,[22] these were reduced *in situ* to the corresponding alcohols by $NaBH_4$ (Scheme 3) once the starting material **7** had disappeared (TLC monitoring). Interestingly, the alcohols deriving from the reduction of isomers **8'** were not observed when adopting this two-step procedure. Thus, in the presence of *t*-

$Bu_3PAuNTf_2$ as the catalyst, **7a** was quantitatively converted to alcohol **10a**, which was obtained in 72% yield after chromatography. With compound **7b**, bearing a *n*-Bu chain, the reaction carried out with the same catalyst was sluggish, providing after 16 h a mixture of alcohol **10b** (63%) and the corresponding allene (29%), together with traces of unreacted starting material (8%). Instead, with the IPrAuOTf catalyst the reaction was faster (reaction complete in 4 h) – although still slower than with substrate **7a** – providing alcohol **10b** only, which was isolated in 71% yield. With *gem*-dimethyl substituted **7c** the reaction quantitatively led to Nazarov product **10c** (81% yield) in 1 h, with one double bond obviously forced at the ring junction. No [1,2-CH_3]-shift did take place. Interestingly, with substrate **7h** bearing the same *gem*-dimethyl moiety, and in which the N atom is not conjugated with the endocyclic double bond, the reaction carried out with *t*-$Bu_3PAuNTf_2$ provided alcohol **10h** in 81% yield but as a 1.2:1 mixture of isomers (see Supporting Information).

Scheme 3. Scope of the reaction

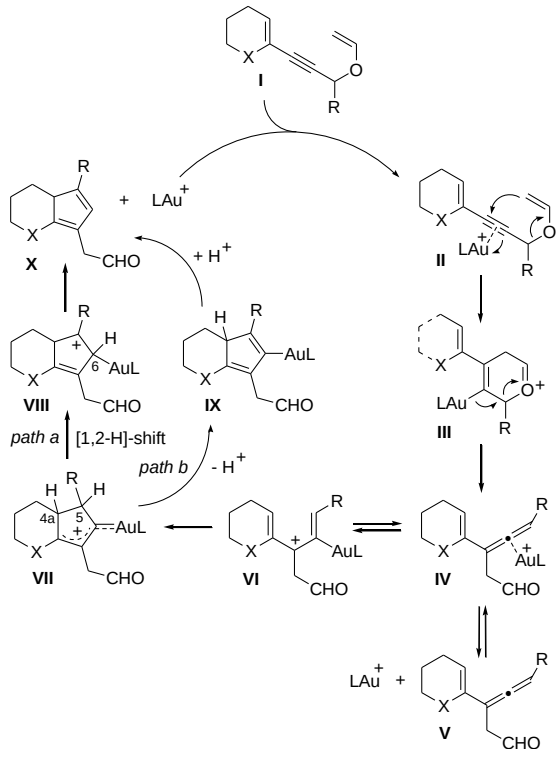


[a]Carried out at 0 °C. [b]21:1 isomeric mixture at 100% conversion. [c]Carried out with 1.5 mol % of catalyst.

With a phenyl-substituted propargylic moiety (substrate **7d**) the reaction was much cleaner when carried out at 0 °C and it provided, after 3.5 h and in situ reduction, alcohol **10d** in 60% yield. Also with the seven-membered ring containing substrates, the presence of the *n*-Bu chain in **7f** relented the reaction (compared to **7e**) when catalyzed by the *t*-$Bu_3PAuNTf_2$ complex, as it was complete in 2 h and provided **10f** in mixture with about 10% of the corresponding allene. With the IPrAuOTf catalyst, the reaction was faster (0.5 h) and provided **10f** only (74% yield after chromatography). Quite interestingly, with these seven-membered ring derivatives, isomerization of the double bonds occurred to form thermodynamically more stable compounds **10e-f**.[24] Finally, as in the case of **7c**, also with substrate **7g** the corresponding product (**10g**) with the double bond at the ring junction was obtained (74% yield) after 6 h in the presence of the IPrAuOTf catalyst.

To demonstrate that this cascade process can be extended to carbacyclic systems, substrates **7i-k**, were subjected to various reaction conditions. While in the case of N-heterocycle alcohol **10a** (as well as **10b** and **10d**) we never observed double bond isomerization in the five-membered ring during the chromatographic purification on silica gel,[25] this was not the case of the products deriving from carbacycle substrates, for the purification of which eluents containing Et_3N had to be used. So, with both **7i** and **7j**, the reaction, best carried out in the presence of 3 mol % $IPrAuSbF_6$, was very fast (complete in 10-20 min) and provided, after reduction, isomerically pure alcohols **10i-j** in excellent yields after chromatography (81-96%). With cycloheptene derivative **7k**, the reaction was even faster at 25 °C and it was thus carried with 1.5 mol % of $IPrAuSbF_6$, quantitatively providing **10k** as a 21:1 mixture with a minor isomer having one double bond at the ring junction.

Scheme 4. Plausible reaction mechanism

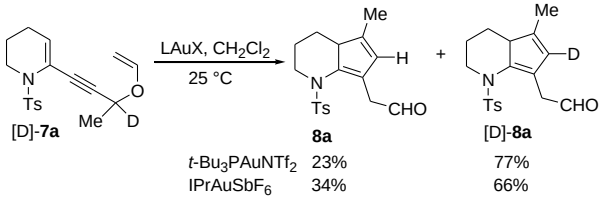


However, this compound proved isomerically less stable as the relative amount of the major isomer gradually decreased in solution (both in $CDCl_3$ and in CD_3OD) during NMR analysis (see Supporting Information).

As the cyclopenta[b]indole motif is present in several natural and synthetic biologically active compounds,[26-27] the scope of the process was evaluated with some indole derivatives, too (compounds **7l-o**). Thus, the cascade process provided substituted cyclopenta[b]indoles **10l-o** (58-65% yield) in which isomerization of the double bond occurred to restore the aromaticity of the indole ring. With substrate **7l**, the reaction was complete in 2 h with $IPrAuSbF_6$ (3 mol %) as the catalyst, whereas with the *gem*-dimethyl-substituted propargylic derivative **7n**, 5 h were necessary for a complete conversion with the same catalyst. Both *n*-butyl-substituted derivative **7m** and Br-substituted indole **7o** were instead best reacted in the presence of IPrAuOTf (3 mol %) as the catalyst.

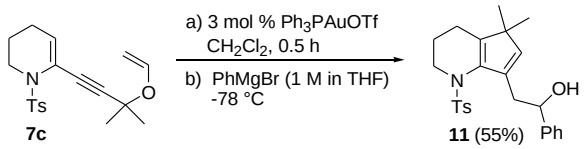
The proposed catalytic cycle for this tandem process is reported in Scheme 4. The initial coordination of gold to the triple bond triggers the [3,3]-rearrangement to form allene-gold complex **IV**. Gold(I)-complex **IV** then evolves toward allene **V** or rearranges to pentadienyl cation **VI** which cyclizes to give intermediate **VII**. The position of the double bonds in the final product **X** seems consistent with the mechanism proposed by Toste for the cycloisomerization of vinyl allenes,[7] i.e. a [1,2-H]-shift from position 5 to 6 in **VII** to generate cation **VIII** (*path a*) and eventual LAu^+ elimination. However, in an experiment carried out with deuterated **7a** ([D]-**7a**, Scheme 5) in the presence of 3 mol % *t*-$Bu_3PAuNTf_2$ only 77% of deuterium was incorporated at position 6 of the final product, suggesting that at least with this type of substrates, a mechanism involving deprotonation-protodeauration (*path b*) is also operative. The relative rate seems depending on the type of catalysts used, as incorporation of D at C6 further decreased when using $IPrAuSbF_6$ (Scheme 5).

Scheme 5.



Clearly, with *gem*-dimethyl-substituted substrates like **7c** and **7h**, none of the above mechanisms can be effective and a base-assisted (TfO^-) deprotonation at 4a position followed by protodeauration must instead take place. The fact we never observe the formation of allene **V** in the presence of the IPr ligand (e.g. entries 6-10, Table 1, for **7a**), even when the reaction is slow, suggests that the cyclization of allene-gold complex **IV**, to give the Nazarov product, must be fast once **IV** is formed.[28] The generally much faster cyclization observed when TfO^- is present in the reaction medium could be accounted for by its greater basicity compared to the other anions used in this study,[29] which promotes either the [1,2-H]-shift (proton shuttling) (path a) or deprotonation at C5 (path b) or C4a.

Scheme 6.



Finally, to demonstrate that chain elongation can be carried out in situ, PhMgBr (1 M in THF) was added at -78 °C to the DCM solution containing aldehyde **8c** just after completion of the gold-catalyzed process (Scheme 6). The reaction provided alcohol **11** in 55% yield after chromatography.

In conclusion, we have developed a gold(I)-catalyzed propargyl Claisen rearrangement/Nazarov cyclization cascade process for the synthesis of functionalized cyclopentadienes fused with various *N*-hetero- and carbacycles, including indoles. The reaction occurs under mild conditions and provides, in general, isomerically stable products with high regioselectivity and in good to excellent yields. Depending on the substrate, alternate mechanism pathways are possible after the cyclization step, with the position of the double bonds in the five-membered ring dictated by the type of (hetero)cycle bearing the propargylic moiety and the side chain on the latter. The presence of an aldehyde appendage on the cyclopentadiene allows for further elaboration, even in situ, to increase the complexity of the products. Extension of the methodology to other systems and application to the synthesis of natural compounds is ongoing in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(18) We used a variant of the $Hg(OAc)_2$-catalyzed vinylation reported in ref 17a. See also: Wisniewski Grissom, J.; Klingberg, D.; Huang, D.; Slattery, B. J. *J. Org. Chem*. **1997**, *62*, 603.

(19) Vinyl ethers **7** were not stable when neat and they were better stored in the chromatographic eluent containing 1% Et_3N until their use.

(20) The structure of compound **8a** was easily determined by ^{1}H NMR studies. The aldehyde proton resonates at 9.76 ppm as a singlet, the α hydrogens to the carbonyl group form an AB system at 3.73 and 3.41 ppm. 6-H is a singlet at 6.01 ppm and the methyl group a singlet at 1.86 ppm. The bridgehead 4a-H resonates at 2.00 ppm and couples with protons at C4. Its isomer **8a'** has the singlet of 6-H at about 6.15 ppm and the aldehyde H resonates at 9.77 ppm. Bridgehead 7a-H is a singlet at about 3.65 ppm.

(21) Diagnostic ^{1}H NMR signals of allene **9a** are the quartet at 4.6 ppm and the doublet at 1.8 ppm (=CH and Me group of the allene moiety, respectively), and the triplet at 5.48 ppm of 3-H (heterocycle). The aldehyde proton resonates as a triplet at 9.7 ppm and the α hydrogens as a multiplet at 3.32 ppm.

(22) Aldehydes **8** tend to form various unidentified by-products during chromatography on silica gel, which lowers the yield of the isolated products. In some cases migration of the double bond to the exocyclic position also occurs during chromatography to generate the corresponding α,β-unsaturated aldehydes (*iso*-**8**) but in impure form (see Supporting Information). For this reason, in situ reduction to corresponding alcohols **10** was carried before work up to obtain stable compounds.

(23) We monitored this reaction by ^{1}H NMR at 10, 30, 60 and 120 min but never observed even traces of allene **9a**.

(24) RHF/3-21G(*) calculations (PC Spartan Pro software, Wavefunction, Inc.) resulted in compound **10e** being 8.9 kcal/mol lower in energy than its isomer with double bonds at C6-C7 and C8-C8a.

(25) In compound **10a** (and analogues) there is a fully conjugated π system, from the N atom to C5, which stabilizes this isomer.

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(27) For other approaches to pentannulated indoles which exploit gold(I) catalysis, see: (a) Mei, L.-Y.; Wei, Y.; Tang, X.-Y.; Shi, M. *J. Am. Chem. Soc*. **2015**, *137*, 8131. (b) Alcaide, B.; Almendros, P.; Alonso, J. M.; Fernández, I. *J. Org. Chem*. **2013**, *78*, 6688. (c) Ma,

Z.-X.; He, S.; Song, W.; Hsung, R. P. *Org. Lett*. **2012**, *14*, 5736. (d) Dhiman, S.; Ramasastry, S. S. V. *Org. Lett*. **2015**, *17*, 5116. (e) Dhiman, S.; Ramasastry, S. S. V. *Chem. Commun*. **2015**, *51*, 557. (f) Kothandaraman, P.; Rao, W.; Foo, S. J.; Chan, P. W. H. *Angew. Chem., Int. Ed*. **2010**, *49*, 4619. See also refs 9c, 12b and 26a.

(28) When product mixtures containing allene **9a** were treated with the IPrAuOTf catalyst under the optimized reaction conditions, conversion of the allene into **8a** occurred but it was much slower than the conversion of **7a**, reasonably for the minor "allenophilicity" of the LAu^+ species compared to its "alkynophilicity".

(29) (a) Lu, Z.; Han, J.; Okoromoba, O. E.; Shimuzu, N.; Amii, H.; Tormena, C. F.; Hammond, G. B.; Xu, B. *Org. Lett.* **2017**, *19*, 5848. For a review on counterion effects in homogeneous gold catalysis see: (b) Jia, M.; Bandini, M. *ACS Catalysis*, **2015**, *5*, 1638.